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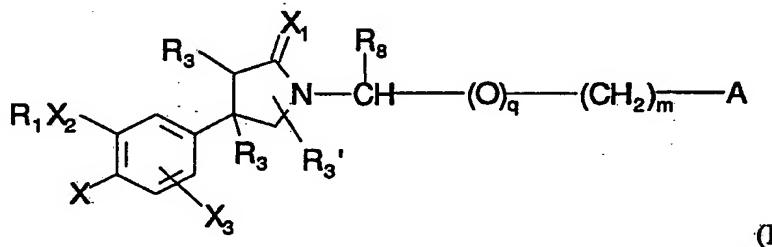
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(54) Title: HETEROCYCLIC 3-PHENYL PYRROLIDIN-2-ONES, THEIR PREPARATION AND USE FOR THE MANUFACTURE OF A MEDICAMENT FOR INHIBITING TUMOR NECROSIS FACTOR PRODUCTION



(57) Abstract

A compound of formula (I), wherein the substituents are as defined in the claims inhibits the production of tumor necrosis factor (TNF).

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HETEROCYCLIC 3-PHENYL PYRROLIDIN-2-ONES, THEIR PREPARATION AND USE FOR THE MANUFACTURE OF A MEDICAMENT FOR INHIBITING TUMOR NECROSIS FACTOR PRODUCTION

Field of Invention

5 The present invention relates to novel heterocyclic pyrrolidinones, pharmaceutical compositions containing these compounds and their use in treating allergic and inflammatory diseases and for inhibiting the production of Tumor Necrosis Factor (TNF).

10 Background of the Invention

Bronchial asthma is a complex, multifactorial disease characterized by reversible narrowing of the airway and hyperreactivity of the respiratory tract to external stimuli.

15 It is now understood that the symptoms of chronic asthma are the manifestations of three distinct processes: 1) an early response to antigen, 2) a delayed or late response to antigen, and 3) chronic inflammation and airway hyperreactivity. Cockcroft, Ann. Allergy 55:857-862, 1985; Larsen, Hosp. Practice 22:113-127, 1987. The agents currently available ( $\beta$ -adrenoceptor agonists, steroids, methylxanthines, disodium cromoglycate) are inadequate to control the disease; none 20 of them modify all three phases of asthma and nearly all are saddled with limiting side effects. Most importantly, none of the agents, with the possible exception of steroids, alter the course of progression of chronic asthma.

25 Identification of novel therapeutic agents for asthma is made difficult by the fact that multiple mediators are responsible for the development of disease. Thus, it seems unlikely that eliminating the effects of a single mediator will have a substantial effect on all three components of chronic asthma. An alternative to the "mediator approach" is to regulate the activity of the cells responsible for the pathophysiology of the disease.

30 One such way is by elevating levels of cAMP (adenosine cyclic 3',5'-monophosphate). Cyclic AMP has been shown to be a second messenger mediating the biologic responses to a wide range of hormones, neurotransmitters and drugs (Robison *et al.*, Cyclic AMP Academic Press, New York, pgs. 17-47, 1971; Krebs Endocrinology Proceedings of the 4th International Congress Excerpta Medica, pgs. 17-29, 1973). When the appropriate agonist binds to specific cell surface receptors, 35 adenylate cyclase is activated which converts  $Mg^{2+}$ -ATP to cAMP at an accelerated rate. The actions of cAMP are terminated by cyclic nucleotide phosphodiesterases (PDEs), which hydrolyze the 3'-phosphodiester bond to form 5'-AMP, an inactive metabolite.

Cyclic AMP modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma. As such, an elevation of cAMP would produce beneficial effects including: 1) airway smooth muscle relaxation, 2) inhibition of mast cell mediator release, 3) suppression of 5 neutrophil degranulation, 4) inhibition of basophil degranulation, and 5) inhibition of monocyte and macrophage activation. Hence, compounds that activate adenylate cyclase or inhibit PDE should be effective in suppressing the inappropriate activation of airway smooth muscle and a wide variety of inflammatory cells. The 10 principal cellular mechanism for the inactivation of cAMP is hydrolysis of the 3'- phosphodiester bond by one or more of a family of isozymes referred to as cyclic nucleotide phosphodiesterases (PDEs).

It has now been shown that a distinct cyclic nucleotide phosphodiesterase (PDE) isozyme, PDE IV, is responsible for cyclic AMP breakdown in airway smooth muscle and inflammatory cells. Torphy, "Phosphodiesterase Isozymes: 15 Potential Targets for Novel Anti-asthmatic Agents" in New Drugs for Asthma, Barnes, ed. IBC Technical Services Ltd. (1989). Research indicates that inhibition of this enzyme not only produces airway smooth muscle relaxation, but also suppresses degranulation of mast cells, basophils and neutrophils along with inhibiting the activation of monocytes and neutrophils. Moreover, the beneficial 20 effects of PDE IV inhibitors are markedly potentiated when adenylate cyclase activity of target cells is elevated by appropriate hormones or autocoids, as would be the case in vivo. Thus PDE IV inhibitors would be effective in the asthmatic lung, where levels of prostaglandin E<sub>2</sub> and prostacyclin (activators of adenylate cyclase) are elevated. Such compounds would offer a unique approach toward the 25 pharmacotherapy of bronchial asthma and possess significant therapeutic advantages over agents currently on the market.

The compounds of this invention also inhibit production of Tumor Necrosis Factor (TNF), a serum glycoprotein. Excessive or unregulated TNF production is implicated in mediating or exacerbating a number of diseases including rheumatoid 30 arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias 35 due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

TNF has been implicated in various roles with the human acquired immune deficiency syndrome (AIDS). AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). It has now been discovered that monokines, specifically TNF, are implicated in the infection of T lymphocytes with

5 HIV by playing a role in maintaining T lymphocyte activation. Furthermore, once an activated T lymphocytes is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. It has also been discovered that monokines, specifically TNF, are implicated in activated T cell-mediated HIV protein expression and/or virus

10 replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with monokine activity such as by inhibition of monokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of

15 immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg et al., The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been

20 shown to activate HIV replication in monocytes and/or macrophages [See Poli, et al., Proc. Natl. Acad. Sci., 87:782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T cells.

It has now been discovered that monokines are implicated in certain disease-

25 associated problems such as cachexia and muscle degeneration. Therefore, interference with monokine activity, such as by inhibition of TNF production, in an HIV-infected individual aids in enhancing the quality of life of HIV-infected patients by reducing the severity of monokine-mediated disease associated problems such as cachexia and muscle degeneration.

30 TNF is also associated with yeast and fungal infections. Specifically *Candida Albicans* has been shown to induce TNF production *in vitro* in human monocytes and natural killer cells. [See Riipi et al., Infection and Immunity, Vol. 58, No. 9, p. 2750-54 (1990); and Jafari et al., Journal of Infectious Diseases, Vol. 164, p. 389-95 (1991). See also Wasan et al., Antimicrobial Agents and

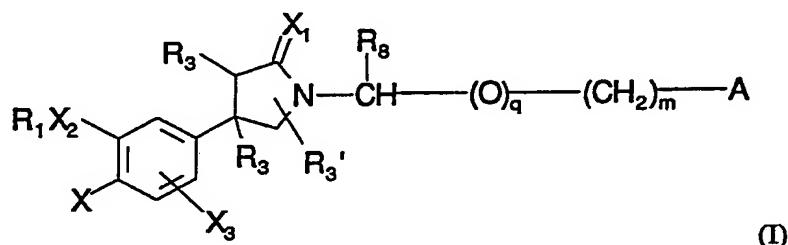
35 Chemotherapy, Vol. 35, No. 10, p. 2046-48 (1991) and Luke et al., Journal of Infectious Diseases, Vol. 162, p. 211-214 (1990)].

The discovery of a class of compounds which inhibit the production of TNF will provide a therapeutic approach for the diseases in which excessive, or unregulated TNF production is implicated.

5

Summary of the Invention

The compounds of this invention are illustrated by the formula (I)



10 wherein:

R<sub>1</sub> is C<sub>1-12</sub> alkyl unsubstituted or substituted by 1 or more halogens, C<sub>3-6</sub> cycloalkyl unsubstituted or substituted by 1 to 3 methyl groups or an ethyl group; C<sub>4-6</sub> cycloalkenyl containing one or two unsaturated bonds; C<sub>7-11</sub> polycycloalkyl, -(CR<sub>14</sub>R<sub>14</sub>)<sub>n</sub>C(O)O-(CR<sub>14</sub>R<sub>14</sub>)<sub>m</sub>-R<sub>10</sub>, -(CR<sub>14</sub>R<sub>14</sub>)<sub>n</sub>C(O)O-(CR<sub>14</sub>R<sub>14</sub>)<sub>r</sub>-R<sub>11</sub>, -(CR<sub>14</sub>R<sub>14</sub>)<sub>x</sub>OH, -(CR<sub>14</sub>R<sub>14</sub>)<sub>s</sub>O(CR<sub>14</sub>R<sub>14</sub>)<sub>m</sub>-R<sub>10</sub>, -(CR<sub>14</sub>R<sub>14</sub>)<sub>s</sub>O(CR<sub>14</sub>R<sub>14</sub>)<sub>r</sub>-R<sub>11</sub>, -(CR<sub>14</sub>R<sub>14</sub>)<sub>n</sub>-(C(O)NR<sub>14</sub>)-(CR<sub>14</sub>R<sub>14</sub>)<sub>m</sub>-R<sub>10</sub>, (CR<sub>14</sub>R<sub>14</sub>)<sub>n</sub>-(C(O)NR<sub>14</sub>)-(CR<sub>14</sub>R<sub>14</sub>)<sub>r</sub>-R<sub>11</sub>, -(CR<sub>14</sub>R<sub>14</sub>)<sub>y</sub>-R<sub>11</sub> or -(CR<sub>14</sub>R<sub>14</sub>)<sub>z</sub>-R<sub>10</sub>;

X<sub>1</sub> is O or S;

X<sub>2</sub> is O or NR<sub>14</sub>;

20 X<sub>3</sub> is hydrogen or X;

X is YR<sub>2</sub>, halogen, nitro, NR<sub>14</sub>R<sub>14</sub> or formamide;

Y is O or S(O)m;

R<sub>2</sub> is -CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>3</sub>, each may be unsubstituted or substituted by 1 to 5 fluorines;

25 R<sub>3</sub> is independently hydrogen, halogen, CN, C<sub>1-4</sub>alkyl, halo-substituted C<sub>1-4</sub>alkyl, cyclopropyl unsubstituted or substituted by R<sub>9</sub>, OR<sub>5</sub>, -CH<sub>2</sub>OR<sub>5</sub>, -NR<sub>5</sub>R<sub>16</sub>, -CH<sub>2</sub>NR<sub>5</sub>R<sub>16</sub>, -C(O)OR<sub>5</sub>, -C(O)NR<sub>5</sub>R<sub>16</sub>, -CH=CR<sub>9</sub>R<sub>9</sub>, -C≡CR<sub>9</sub>, or -C(Z)H;

R<sub>3'</sub> is hydrogen, halogen, C<sub>1-4</sub>alkyl, halo-substituted C<sub>1-4</sub>alkyl, cyclopropyl unsubstituted or substituted by R<sub>9</sub>, -CN, -CH<sub>2</sub>OR<sub>5</sub>, -CH<sub>2</sub>NR<sub>5</sub>R<sub>16</sub>, -C(O)OR<sub>5</sub>,

30 -C(O)NR<sub>5</sub>R<sub>16</sub> or -C(Z)H;

A is (2-, 3-, or 4-pyridyl), 4-morpholinyl, 4-piperidinyl, (1-, 2-, 4- or 5-imidazolyl), (2- or 3-thienyl), (2- or 5-pyrimidyl) or (4 or 5-thiazolyl) all of which may be unsubstituted or substituted by one or more: Br, F, Cl, NR<sub>5</sub>R<sub>16</sub>, NR<sub>6</sub>R<sub>16</sub>.

NO<sub>2</sub>, -COR<sub>7</sub>, -S(O)<sub>m</sub>R<sub>12</sub>, CN, OR<sub>5</sub>, -OC(O)NR<sub>5</sub>R<sub>16</sub>, (1- or 1-(R<sub>5</sub>)-2-imidazolyl), -C(NR<sub>16</sub>)NR<sub>5</sub>R<sub>16</sub>, -C(NR<sub>5</sub>)SR<sub>12</sub>, -OC(O)R<sub>5</sub>, -C(NCN)NR<sub>5</sub>R<sub>16</sub>, -C(S)NR<sub>5</sub>R<sub>16</sub>, -NR<sub>16</sub>C(O)R<sub>15</sub>, oxazolyl, thiazolyl, pyrazolyl, triazolyl or tetrazolyl; or when R<sub>5</sub> and R<sub>16</sub> are as NR<sub>5</sub>R<sub>16</sub> they may together with the nitrogen form a 5 to 7

5 membered ring optionally containing at least one additional heteroatom selected from O, N or S; or A is SR<sub>12</sub>;

R<sub>5</sub> is independently hydrogen or C<sub>1-4</sub>alkyl, unsubstituted or substituted by one to three fluorines;

R<sub>6</sub> is R<sub>5</sub>, -C(O)R<sub>5</sub>, -C(O)C(O)R<sub>7</sub>, -C(O)NR<sub>5</sub>R<sub>16</sub>, -S(O)<sub>m</sub>R<sub>12</sub>, -C(NCN)SR<sub>12</sub>, -C(NCN)NR<sub>5</sub>R<sub>16</sub>, -C(NCN)R<sub>12</sub>, -C(NR<sub>16</sub>)R<sub>12</sub> or -C(NR<sub>16</sub>)SR<sub>12</sub>;

R<sub>7</sub> is OR<sub>5</sub>, -NR<sub>5</sub>R<sub>16</sub> or R<sub>12</sub>;

R<sub>8</sub> is hydrogen, C(O)R<sub>7</sub>, (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl-[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]), (2-, 4-, or 5-thiazolyl), (2-, 4-, or 5-oxazolidinyl), (2-, 4-, or 5-thiazolidinyl) or (2-, 4-, or 5-imidazolidinyl), wherein each of the heterocyclic ring systems may be optionally substituted by one or more R<sub>14</sub> groups;

R<sub>9</sub> is hydrogen, F or R<sub>12</sub>;

R<sub>10</sub> is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC<sub>1-3</sub>alkyl, halo substituted aryloxyC<sub>1-3</sub>alkyl, indanyl, indenyl, C<sub>7-11</sub> polycycloalkyl, furanyl, pyranyl, thienyl, thiopyranyl, (3- or 4-tetrahydrothiopyranyl), 3-tetrahydrafuranyl, 3-tetrahydrothienyl, (3- or 4-tetrahydropyranyl), C<sub>3-6</sub> cycloalkyl or a C<sub>4-6</sub>cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R<sub>11</sub> is 2-tetrahydropyranyl or 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl or 2-tetrahydrothienyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R<sub>12</sub> is C<sub>1-4</sub>alkyl unsubstituted or substituted by one to three fluorines;

30 R<sub>14</sub> is independently hydrogen or a C<sub>1-2</sub>alkyl unsubstituted or substituted by fluorine;

R<sub>15</sub> is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl or pyrrolyl, and each of the heterocyclics may be unsubstituted or substituted by one or two C<sub>1-2</sub>alkyl groups;

R<sub>16</sub> is OR<sub>5</sub> or R<sub>5</sub>;

Z is O, NR<sub>12</sub>, NOR<sub>5</sub>, NCN, C(-CN)<sub>2</sub>, CR<sub>5</sub>NO<sub>2</sub>, CR<sub>5</sub>C(O)OR<sub>5</sub>, CR<sub>5</sub>C(O)NR<sub>5</sub>R<sub>5</sub>, C(-CN)NO<sub>2</sub>, C(-CN)C(O)OR<sub>12</sub> or C(-CN)C(O)NR<sub>5</sub>R<sub>5</sub>;

m is an integer from 0 to 2;  
n is an integer from 1 to 4;  
q is an integer from 0 to 1;  
r is an integer from 1 to 2;  
5 s is an integer from 2 to 4;  
x is an interger from 2 to 6;  
y is an integer from 1 to 6;  
z is an integer from 0 to 6;  
or a pharmaceutically acceptable salt thereof;

10 provided that m is 2 when R<sub>10</sub> is OH in -(CR<sub>14</sub>R<sub>14</sub>)<sub>n</sub>-C(O)O-(CR<sub>14</sub>R<sub>14</sub>)<sub>m</sub>R<sub>10</sub>, -(CR<sub>14</sub>R<sub>14</sub>)<sub>n</sub>(C(O)NR<sub>14</sub>)(CR<sub>14</sub>R<sub>14</sub>)<sub>m</sub>R<sub>10</sub> or  
C(R<sub>14</sub>R<sub>14</sub>)<sub>s</sub>O(CR<sub>14</sub>R<sub>14</sub>)<sub>m</sub>R<sub>10</sub>, and further provided that z is 2 to 6 when R<sub>10</sub> is  
OH in -(CR<sub>14</sub>R<sub>14</sub>)<sub>2</sub>R<sub>10</sub>, and further provided that m is 1 or 2 when A is SR<sub>12</sub>.

15 In a second aspect, this invention relates to a pharmaceutical composition containing a compound of formula I in admixture with a pharmaceutically excipient.

This invention further constitutes a method of inhibiting phosphodiesterase IV in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of Formula (I).

20 This invention further constitutes a method of inhibiting the production of TNF in an animal, including humans, which comprises administering to an animal in need thereof, an effective amount of a compound of Formula (I).

#### Detailed Description of the Invention

25 Phosphodiesterase IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases including: asthma, chronic bronchitis, atopic dermatitis, urticardia, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In 30 addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus, (Kidney Int. 37:362, 1990; Kidney Int. 35:494, 1989) and central nervous system disorders such as depression and multi-infarct dementia.

These compounds can also be used to treat a human afflicted with a human immunodeficiency virus (HIV), AIDS Related Complex (ARC) or any other disease 35 state associated with an HIV infection, which comprises administering to such a human an effective TNF inhibiting amount of a compound of Formula (I).

The present invention also provides a method of preventing a TNF mediated disease state in an animal in need thereof, including humans, by prophylactically administering an effective amount of a compound of Formula I.

The compounds of the present invention are also useful in the treatment of 5 additional viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. The viruses contemplated for treatment herein are those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (I). Such viruses include, but are not limited to; HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, 10 adenovirus and the Herpes group of viruses, such as, Herpes Zoster and Herpes Simplex.

The compounds of Formula (I) are also useful in the treatment of yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. A preferred disease state for treatment is 15 fungal meningitis. Additionally, the compounds of the Formula (I) may be administered in conjunction with other drugs of choice, either simultaneously or in a consecutive manner, for systemic yeast and fungal infections. Drugs of choice for fungal infections, include but are not limited to the class of compounds called the polymixins, such as Polymycin B, the class of compounds called the imidazoles, 20 such as clotrimazole, econazole, miconazole, and ketoconazole; the class of compounds called the triazoles, such as fluconazole, and itraconazole, and the class of compound called the Amphotericins, in particular Amphotericin B and liposomal Amphotericin B.

The preferred organism for treatment is the *Candida* organism. The 25 compounds of the Formula (I) may be co-administered in a similar manner with anti-viral or anti-bacterial agents.

The compounds of the Formula (I) may also be used for inhibiting and/or reducing the toxicity of an anti-fungal, anti-bacterial or anti-viral agent by 30 administering an effective amount of a compound of the Formula (I) to a mammal in need of such treatment. Preferably, a compound of the Formula (I) is administered for inhibiting or reducing the toxicity of the Amphotericin class of compounds, in particular Amphotericin B.

Also included in this invention are pharmaceutically acceptable salt complexes of the compounds of this invention which can form salts.

35 All defined alkyl groups can be straight or branched.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are contemplated to be within the scope of the present

invention. The term "halogen" is used to mean chloro, fluoro, bromo or iodo. Alkyl groups may be substituted by one or more halogens up to being perhalogenated.

By the term "cycloalkyl" as used herein is meant to include groups of 3-6 carbon atoms, such as cyclopropyl, cyclopropylmethyl, cyclopentyl or cyclohexyl.

5 By the term "aryl" or "aralkyl", unless specified otherwise, as used herein is meant an aromatic ring or ring system of 6-10 carbon atoms, such as phenyl, benzyl, phenethyl or naphthyl. Preferably the aryl is monocyclic, i.e., phenyl.

Examples of C<sub>7</sub>-11 polycycloalkyl are bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, tricyclo [5.2.1.0<sup>2,6</sup>]decyl, etc., additional 10 examples of which are described in Saccamano *et al.*, WO 87/06576, published 5 November 1987 whose disclosure is incorporated herein by reference in its entirety.

Examples of rings when R<sub>5</sub> and R<sub>16</sub> in the moiety -NR<sub>5</sub>R<sub>16</sub> together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing at least one additional heteroatom selected from O/N/ and S include, but 15 are not limited to 1-imidazolyl, 1-pyrazolyl, 1-triazolyl, 2-triazolyl, tetrazolyl, 2-tetrazolyl, morpholinyl, piperazinyl, or pyrrolyl ring.

The invention further provides for the novel pharmaceutical compositions of the compounds of Formula I.

20 The invention provides a method of inhibiting PDE IV which comprises administering to a subject in need thereof, a compound of Formula (I).

The invention further provides a method for the treatment of allergic and inflammatory disease which comprises administering to a subject in need thereof, an effective amount of a compound of Formula (I).

25 The invention also provides a method for the treatment of asthma which comprises administering to a subject in need thereof, an effective amount of a compound of Formula (I).

The compounds of Formula (I) are useful in treating, prophylactically or therapeutically, disease states in humans which are exacerbated or caused by excessive or unregulated TNF production.

30 Therefore, the present invention also provides a method for the inhibition of the production of tumor necrosis factor (TNF) in an animal in need thereof, including humans, which comprises administering to the animal in need of such treatment an effective amount of a compound of Formula I.

35 By the term "inhibiting the production of TNF" is meant a) a decrease of excessive *in vivo* TNF levels in a human to normal levels or below normal levels by inhibition of the *in vivo* release of TNF by all cells, including but not limited to monocytes or macrophages;

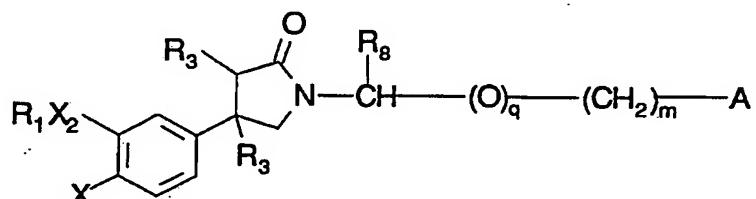
- b) a down regulation, at the translational or transcription level, of excessive *in vivo* TNF levels in a human to normal levels or below normal levels; or
- c) a down regulation, by inhibition of the direct synthesis of TNF as a posttranslational event.

5 By the term "TNF mediated disease states" is meant any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1, or IL-6. A disease state in which IL-1, for instance is a major component, and whose production or action is exacerbated or which is secreted in response to TNF, would therefore be  
10 considered a disease state mediated by TNF.

By the term "cytokine" as used herein is meant any secreted polypeptide that affects the functions of other cells, and is a molecule which modulates interactions between cells in the immune or inflammatory response. A cytokine includes, but is not limited to monokines and lymphokines regardless of which cells produce them.

15 For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte but many other cells produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes, and b-lymphocytes. Lymphokines are generally referred to as being  
20 produced by lymphocyte cells. Examples of cytokines for the present invention include, but are not limited to Interleukin-1 (IL-1), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF $\alpha$ ) and Tumor Necrosis Factor beta (TNF $\beta$ ).

A preferred subgroup of Formula (I) is Formula (Ia):



(Ia)

wherein:

R<sub>1</sub> is phenyl, benzyl or C<sub>1-2</sub> alkyl unsubstituted or substituted by 1 or more fluorines; C<sub>4-6</sub> cycloalkyl, CH<sub>2</sub>-cyclopentyl, CH<sub>2</sub>-cyclopropyl, C<sub>7-11</sub> polycycloalkyl, 3-tetrahydrofuryl, cyclopentenyl, -(CH<sub>2</sub>)<sub>n</sub>C(O)-O-(CH<sub>2</sub>)<sub>m</sub>CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>2-4</sub>OH, -(CH<sub>2</sub>)<sub>s</sub>O(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>n</sub>-(C(O)NR<sub>14</sub>)-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>, all of which may be substituted by 1 to 3 methyl groups or one ethyl group;

s is 2 to 4;

m is 0 to 2;

n is 1 - 3;

X is YR<sub>2</sub>, halogen, nitro, amine, C<sub>1-2</sub>dialkylamine, C<sub>1-2</sub>monoalkylamine or formamide;

Y is O or S(O)<sub>m</sub>;

5 R<sub>2</sub> is -CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>3</sub>, each may be unsubstituted or substituted by 1 to 4 fluorines;

R<sub>3</sub> is independently hydrogen, CF<sub>2</sub>H, CH<sub>2</sub>F, -CH<sub>2</sub>OR<sub>5</sub>, C(O)OR<sub>5</sub>, C(O)NR<sub>5</sub>R<sub>5</sub>, C(O)H, C(NOR<sub>5</sub>)H, CH<sub>3</sub>, CN, F, OH, -C≡CR<sub>9</sub> or CF<sub>3</sub>;

10 q is 0 or 1;

10 A is (2-, 3-, or 4-pyridyl), 4-morpholinyl, 4-piperidinyl, (1- or 2-imidazolyl), (2- or 3-thienyl) or (4- or 5-thiazolyl), all of which may be unsubstituted or substituted by one or more: Br, F, Cl, -NR<sub>5</sub>R<sub>6</sub>, NR<sub>5</sub>R<sub>16</sub>, NR<sub>6</sub>R<sub>16</sub>, NO<sub>2</sub>, -COR<sub>7</sub>, -S(O)<sub>m</sub>R<sub>12</sub>, CN, OR<sub>5</sub>, -OC(O)NR<sub>5</sub>R<sub>16</sub>, (1- or 2-imidazolyl), -C(NR<sub>16</sub>)NR<sub>5</sub>R<sub>16</sub>, -C(NR<sub>5</sub>)SR<sub>12</sub>, -OC(O)R<sub>5</sub>, -C(NCN)NR<sub>5</sub>R<sub>16</sub>, -C(S)NR<sub>5</sub>R<sub>16</sub>, -NR<sub>16</sub>C(O)R<sub>15</sub>,

15 oxazolyl, thiazolyl, pyrazolyl, triazolyl or tetrazolyl; or when R<sub>5</sub> and R<sub>16</sub> are as NR<sub>5</sub>R<sub>16</sub> they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S; or A is SR<sub>12</sub>;

R<sub>5</sub> is independently hydrogen or C<sub>1-4</sub>alkyl, unsubstituted or substituted by

20 one to three fluorines;

R<sub>6</sub> is R<sub>5</sub>, -C(O)R<sub>5</sub>, -C(O)C(O)R<sub>7</sub>, -C(O)NR<sub>5</sub>R<sub>16</sub>, -S(O)<sub>m</sub>R<sub>12</sub>, -C(NCN)S(R<sub>12</sub>) or -C(NCN)NR<sub>5</sub>R<sub>16</sub>;

R<sub>7</sub> is OR<sub>5</sub>, NR<sub>5</sub>R<sub>16</sub> or R<sub>12</sub>;

R<sub>8</sub> is H or -C(O)R<sub>7</sub>;

25 R<sub>9</sub> is R<sub>5</sub>;

R<sub>12</sub> is C<sub>1-4</sub>alkyl unsubstituted or substituted by one to three fluorines;

R<sub>15</sub> is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl or pyrrolyl, and each of the heterocyclics may

30 be unsubstituted or substituted by one or two C<sub>1-2</sub> alkyl groups;

R<sub>16</sub> is OR<sub>5</sub> or R<sub>5</sub>; or a pharmaceutically acceptable salt thereof;

Preferred compounds are those in which X<sub>1</sub> and X<sub>2</sub> are oxygen, A is an optionally substituted (2-, 3- or 4-pyridyl), 4-morpholinyl, 2-thienyl, 2-imidazolyl or 4-thiazolyl; R<sub>1</sub> is CH<sub>2</sub>-cyclopropyl, CH<sub>2</sub>-C<sub>5-6</sub> cycloalkyl, C<sub>4-6</sub> cycloalkyl, phenyl, tetrahydrofuran-3-yl, cyclopentenyl, -C<sub>1-2</sub>alkyl optionally substituted by one or more fluorines, -(CH<sub>2</sub>)<sub>n</sub>C(O)-O-(CH<sub>2</sub>)<sub>m</sub>CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>s</sub>O(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub> or -(CH<sub>2</sub>)<sub>2</sub>-4OH; X is YR<sub>2</sub>, Y is O; R<sub>2</sub> is a C<sub>1-2</sub>alkyl optionally substituted by one or more fluorines; one R<sub>3</sub> is hydrogen and the other R<sub>3</sub> is hydrogen, C≡CR<sub>9</sub>, CN, C(Z)H,

$\text{CH}_2\text{OH}$ ,  $\text{CH}_2\text{F}$ ,  $\text{CF}_2\text{H}$ , or  $\text{CF}_3$ ;  $Z$  is  $\text{O}$  or  $\text{NOR}_5$ ;  $R_3$  is hydrogen;  $X_3$  is hydrogen; and  $A$  is an optionally substituted (2-, 3- or 4-pyridyl), 4-morpholinyl, 2-thienyl, 2-imidazolyl or 4-thiazolyl.

More preferred are compounds in which  $R_1$  is  $\text{C}_1\text{-2}$  alkyl substituted by 1 or 5 more fluorines,  $\text{CH}_2\text{-cyclopropyl}$ ,  $\text{CH}_2\text{-cyclopentyl}$ , cyclopentyl or cyclopentenyl;  $R_2$  is methyl or fluoro substituted  $\text{C}_1\text{-2}$  alkyl;  $R_3$  is hydrogen,  $\text{C}\equiv\text{CH}$  or  $\text{CN}$ ; and  $A$  is 2-, 3- or 4-pyridyl, 4-morpholinyl, 2-thienyl, 2-imidazole or 4-thiazolyl, each of which may be substituted or unsubstituted by  $\text{NR}_5\text{R}_1\text{R}_2$  or  $\text{NR}_5\text{C(O)R}_5$ .

Most preferred are compounds wherein  $R_1$  is cyclopentyl,  $\text{CF}_3$ ,  $\text{CH}_2\text{F}$ , 10  $\text{CHF}_2$ ,  $\text{CF}_2\text{CHF}_2$ ,  $\text{CH}_2\text{CF}_3$ ,  $\text{CH}_2\text{CHF}_2$ ,  $\text{CH}_3$ ,  $\text{CH}_2\text{-cyclopentyl}$ ,  $\text{CH}_2\text{-cyclopropyl}$  or cyclopentenyl;  $R_2$  is  $\text{CH}_3$ ,  $\text{CF}_3$ ,  $\text{CHF}_2$ , or  $\text{CH}_2\text{CHF}_2$ ; one  $R_3$  is hydrogen and the other  $R_3$  is hydrogen,  $\text{C}\equiv\text{CH}$  or  $\text{CN}$  and is in the 4-position.

Especially preferred are the following compounds:

15 1-(2-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,

1-(3-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,

1-(4-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,

20 1-[2-(4-morpholinyl)ethyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,

1-(2-imidazolymethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,

25 (S)-(-)-1-(3-acetamido-4-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,

(S)-(-)-1-(4-acetamido-3-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,

(R)-(+)-1-(3-acetamido-4-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,

30 (R)-(+)-1-(4-acetamido-3-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,

(S)-(-)-1-(2-acetamido-4-thiazolylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,

35 (R)-(+)-1-(2-acetamido-4-thiazolylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,

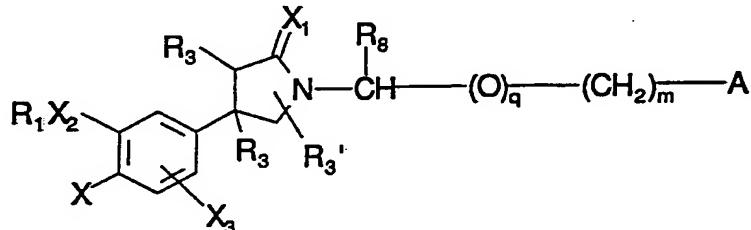
S-(-)-1-(2-acetamido-5-thienylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone,

R-(+)-1-(2-acetamido-5-thienylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone, and  
 4-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-methylthioethyl)-2-pyrrolidinone.

5

General Synthesis

Compounds of the Formula (Ia)

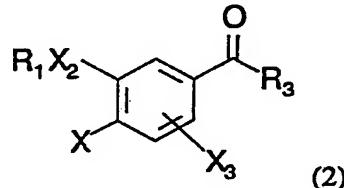


(Ia)

10 can be prepared by a process which comprises:

a) for compounds wherein R3 is H, R12 or cyclopropyl unsubstituted or substituted by R9 and X and X3 are other than S(O)mR2 (wherein m = 1 or 2), Br, I, NO2 or formamide; reacting a compound of the Formula (2)

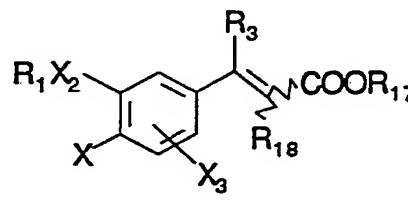
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(2)

wherein X2R1, X and X3 respectively represent X2R1, X and X3 as defined in relation to Formula (I) or groups convertible to X2R1, X and X3, with an appropriate malonic acid ester derivative, such as dimethyl malonate, in a suitable 20 solvent, such as benzene or toluene, at reflux with or without an appropriate catalyst (e.g., titanium tetrachloride or a tertiary amine base with or without added acid) and/or with azeotropic removal of water under an inert atmosphere, to provide a compound of Formula (3) wherein R17 is an alkyl or aryl group and R18 is COOR17;

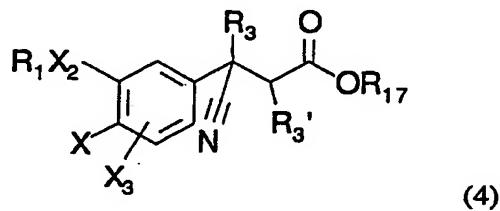
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(3)

Reaction of such a compound of Formula (3) in a suitable solvent, such as an aqueous alcohol, at 25-90°C with a source of cyanide, such as sodium, potassium or tetra-alkylammonium cyanide, provides compounds of the Formula (4)

5

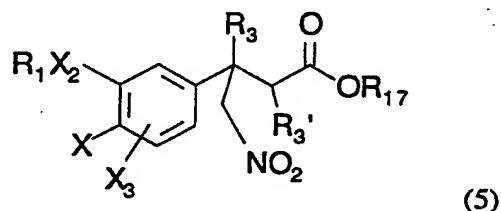


wherein R3' is H or COOR17, typically as a mixture.

Alternatively, reaction of a compound of the Formula (2) with, e.g., 10 carboalkoxy- or carboaryloxy-methylene trialkyl- or triarylphosphorane, provides a compound of the Formula (3) wherein R18 is H. Reaction of such a compound of Formula (3) in a suitable solvent, such as an aqueous alcohol, at 25-90°C with a source of cyanide, such as sodium, potassium or tetraalkylammonium cyanide, also provides compounds of the Formula (4) wherein R3' is H.

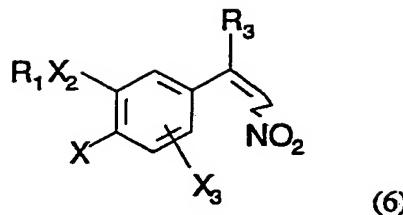
15 Alternatively, reaction of a compound of the Formula (3) wherein R18 is H with the anion of nitromethane generated from an appropriate base or in the presence of an appropriate catalyst, such as alkoxide, a tetraalkylguanidine or a quaternary ammonium halide, in an appropriate solvent, such as an alcohol or nitromethane, provides an ester compound of the Formula (5)

20



wherein R3' is COOR17, which may be hydrolyzed and decarboxylated to provide a compound of the Formula (5) wherein R3' is H. Similarly, compounds of the 25 Formula (5) wherein R3' is H, may be derived from first,

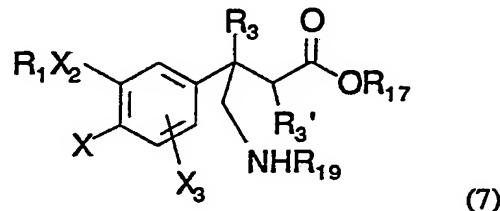
1) reaction of a compound of the Formula (2) with nitromethane as described above to provide a compound of the Formula (6)



followed by 2) further reaction of a such a compound of the Formula (6) with an alkyl or aryl acetate anion, generated at an appropriate temperature (e.g., -78°C) in  
 5 an appropriate solvent (e.g., tetrahydrofuran) using an appropriate base (e.g., lithium diisopropylamide or lithium hexamethyldisilazide).

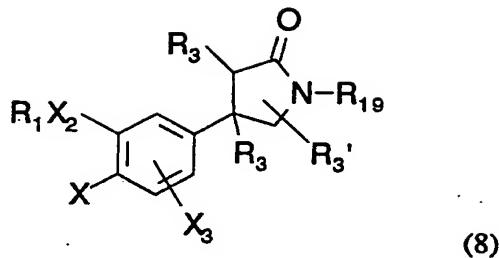
Alternatively, reaction of a compound of the Formula (9) (as described below) wherein R<sub>20</sub> is H and R<sub>3</sub> is H, R<sub>12</sub> or cyclopropyl unsubstituted or substituted by R<sub>9</sub> with a strong base, followed by reaction with an appropriate alkyl 10 or aryl α-halo carboxylate, such as methyl α-bromoacetate, will also provide a compound of the Formula (4) wherein R<sub>3</sub> is H, R<sub>12</sub> or cyclopropyl unsubstituted or substituted by R<sub>9</sub>. Reduction of the nitrile group of such compounds of the above Formula (4) or of the nitro group of the above similar compounds of the Formula (5) provides compounds of Formula (7)

15



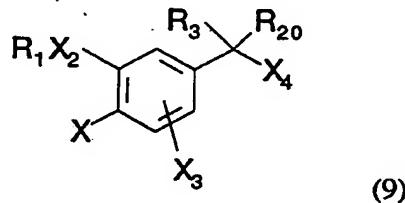
wherein R<sub>19</sub> is H. Reaction of amines of the Formula (7) wherein R<sub>19</sub> is H with an aldehyde in a suitable solvent, such as chloroform at reflux temperature, followed by  
 20 reduction of this imine product with, for example, sodium cyanoborohydride in the presence of an acid in methanol, provides compounds of the Formula (7) wherein R<sub>19</sub> is CH<sub>2</sub>(CH<sub>2</sub>)<sub>m</sub>A; cyclization of such compounds of the Formula (7) then provides the corresponding compounds of Formula (Ia). Alternatively, treatment of compounds of Formula (7) wherein R<sub>19</sub> is H with or without a catalyst in an  
 25 appropriate solvent with an appropriate activated alkylating agent, such as a halide, mesylate or tosylate, provides compounds of the Formula (7) wherein R<sub>19</sub> is CHR<sub>8</sub>(O)<sub>q</sub>(CH<sub>2</sub>)<sub>m</sub>A, which may be cyclized as above to the corresponding compounds of Formula (Ia). In addition, cyclization of above compounds of the Formula (7) wherein R<sub>19</sub> is H provides compounds of the Formula (8)

30



wherein R19 is H; reaction of appropriate compounds of the Formula (8) wherein R19 is H with a strong base, such as sodium hydride, followed by reaction of the 5 generated amide anion with an appropriate activated alkylating agent, such as a halide, mesylate or tosylate, also provides the compounds of the Formula (Ia).

5 b) for compounds wherein R3 is CN and X and X3 are other than S(O)<sub>m</sub>R<sub>2</sub> (wherein m is 1 or 2), Br, I, NO<sub>2</sub> or formyl amine, a sequence beginning with reaction of a compound of the Formula (2) wherein R3 is H with a lithium halide 10 and a silyl halide in an appropriate solvent followed by reduction with an appropriate reductant, such as a siloxane, provides compounds of the Formula (9)



15 15. wherein X4 is chloro or bromo and R3 and R20 are H; alternatively, reduction of a compound of the Formula (2) wherein R3 is H with e.g., sodium borohydride in methanol, provides compounds of the Formula (9) wherein X4 is OH and R3 and R20 are H, which is reacted with, e.g., phosphorous trichloride, thionyl chloride, phosphorus tribromide, cupric bromide or carbon tetrabromide with triphenyl 20 phosphine, to also provide compounds of the Formula (9) wherein X4 is chloro or bromo and R3 and R20 are H. Halide displacement by cyanide then provides compounds of the Formula (9) wherein X4 is CN and R3 and R20 are H, which is allowed to react with a strong base, such as a butyl lithium, at reduced temperature under an inert atmosphere and then may be a) treated with, e.g., anhydrous 25 magnesium bromide, and then reacted with, for example, trimethylsilyl isocyanate and appropriate workup, to produce compounds of Formula (9) wherein R3 is CONH<sub>2</sub>, R20 is H and X4 is CN or b) reacted with, for example, an alkyl or aryl haloformate, such as methyl chloroformate, to produce compounds of the Formula (9) wherein R3 is COOR<sub>17</sub>, R20 is H and X4 is CN; the COOR<sub>17</sub> group of such a

compound may be transformed either at this or a later stage to a CONH<sub>2</sub> group by any of the standard techniques known in the art, such as reaction with concentrated ammonium hydroxide.

Alternatively, a compound of the Formula (9) wherein R<sub>3</sub> is COOR<sub>17</sub>, R<sub>20</sub> is 5 H and X<sub>4</sub> is CN may also be obtained by reaction of a compound of the Formula (9) wherein R<sub>3</sub> and R<sub>20</sub> are H and X<sub>4</sub> is CN with a metal hydride, such as sodium hydride, in the presence of a dialkyl or diaryl carbonate, such as dimethyl carbonate. Also, such compounds may be obtained by homologation of a compound of the Formula (2) wherein R<sub>3</sub> is H to a compound of the Formula (9) wherein R<sub>3</sub> is 10 COOR<sub>17</sub> and X<sub>4</sub> and R<sub>20</sub> are H by any number of known processes, such as reaction with methyl methylsulfinylmethyl sulfide and a base, e.g., sodium hydroxide, followed by treatment with, e.g., alcoholic acid. Generation of an anion of such compounds of the Formula (9) with a suitable base, followed by reaction with, e.g., cyanogen chloride or 2-chlorobenzyl thiocyanate, provides compounds of 15 the Formula (9) wherein R<sub>3</sub> is COOR<sub>17</sub>, R<sub>20</sub> is H and X<sub>4</sub> is CN. Generation of an anion from compounds of the Formula (9) wherein R<sub>20</sub> is H, X<sub>4</sub> is CN and R<sub>3</sub> is CONH<sub>2</sub> or COOR<sub>17</sub> with the appropriate base in an appropriate solvent followed by reaction with an alkyl or aryl  $\alpha$ -halo carboxylate provides a compound of Formula 20 (4) wherein R<sub>3</sub> is CONH<sub>2</sub> or COOR<sub>17</sub>; reduction of the nitrile moiety of such compounds by, for example, hydrogenation with a noble metal or Raney nickel catalyst, provides compounds of the Formula (7) wherein R<sub>19</sub> is H and R<sub>3</sub> is CONH<sub>2</sub> or COOR<sub>17</sub>. The amine moiety of compounds of the Formula (7) wherein R<sub>19</sub> is H and R<sub>3</sub> is CONH<sub>2</sub> is then protected to provide a compound of the Formula 25 (7) wherein R<sub>19</sub> is a protecting group, such as a t-butyloxycarbonyl group, and R<sub>3</sub> is CONH<sub>2</sub>; amide dehydration with, for example, trifluoroacetic anhydride, followed by protecting group removal then provides compounds of the Formula (7) wherein R<sub>19</sub> is H and R<sub>3</sub> is CN, which may then be transformed as described above for other compounds of the Formula (7) to the compounds of the Formula (Ia) wherein R<sub>3</sub> is CN and X and X<sub>3</sub> are other than S(O)<sub>m</sub>R<sub>2</sub> (wherein m = 1 or 2), Br, I, NO<sub>2</sub> or 30 formamide.

c) compounds wherein R<sub>3</sub> of Formula (I) is OR<sub>5</sub> or F and X and X<sub>3</sub> are other than S(O)<sub>m</sub>R<sub>2</sub> (wherein m is 1 or 2), Br, I, NO<sub>2</sub> or formamide are prepared employing a sequence beginning with a cyanohydrin with the hydroxyl suitably protected as a silyl ether, an acetal, or an ester such as a t-BOC. Treatment of a 35 compound of the Formula (2) wherein R<sub>3</sub> is H, R<sub>12</sub> or cyclopropyl unsubstituted or substituted by R<sub>9</sub> with, for example, a derivative of hydrocyanic acid provides the cyanohydrins of Formula (9) wherein R<sub>3</sub> is H, R<sub>20</sub> is OH and X<sub>4</sub> is CN. Subsequent treatment of the Formula (9) compounds with a suitable protecting agent

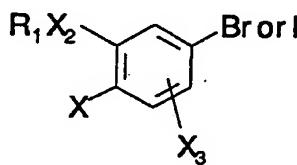
such as trimethylsilyl chloride, di-t-butyldicarbonate and a suitable base, or methyl vinyl ether or direct treatment of the Formula (2) compound with trimethylsilylcyanide and a Lewis Acid provides the protected cyanohydrin of Formula (9) in which R<sub>3</sub> is H, R<sub>20</sub> is the protected hydroxyl and X<sub>4</sub> is CN. The 5 protected cyanohydrin is treated with a strong hindered base, such as LDA, at reduced temperature under an inert atmosphere followed by reaction with, e.g., a bromoacetic acid ester and appropriate workup to produce a compound of Formula (4) wherein R<sub>3</sub> is the protected hydroxyl and R<sub>3'</sub> is H. Reduction of the nitrile moiety of such compounds by, for example, hydrogenation with Raney nickel 10 catalyst, provides Formula (7) compounds wherein R<sub>19</sub> is H and R<sub>3</sub> is the protected or unprotected hydroxyl. These Formula (7) compounds may be alkylated on nitrogen and cyclized as described above, then treated with diethylaminosulfur trifluoride to provide the Formula (Ia) compounds wherein R<sub>3</sub> is F.

15 d) compounds of Formula (Ia) wherein R<sub>3</sub> represents the remaining R<sub>3</sub> groups of Formula (Ia) may be derived from the compounds of the Formulas (8) or (Ia) wherein R<sub>3</sub> is CN by protection of the amide and other sensitive functionality, and manipulation of the CN function as, for example, reduction of the R<sub>3</sub> CN moiety to CHO and functional group transformation of the CHO by any of the standard conditions well known in the art.

20 Some compounds of Formula (Ia) are prepared from other compounds of Formula (Ia) by appropriate manipulation of functional groups present in or as the A, X, X<sub>1</sub>, X<sub>2</sub>R<sub>1</sub>, R<sub>3</sub> or R<sub>3'</sub> moieties.

25 Compounds of Formula (Ia) wherein R<sub>3</sub> is CF<sub>3</sub>, CHF<sub>2</sub> or CH<sub>2</sub>F may be prepared from the corresponding Formula (2) compounds using the methods described above. The formula (2) compounds where R<sub>3</sub> is CF<sub>3</sub> are obtained by the method of Shono et al., J. Org. Chem., Vol. 56, pages 204 (1991) electrochemically from the Formula (2) compounds where R<sub>3</sub> is H.

30 Formula (2) compounds where R<sub>3</sub> is CF<sub>3</sub> or CF<sub>2</sub>H are obtained by treatment of compounds of the Formula (10)



(10)

35 with a metalling agent at -78°C followed by trifluoroacetic acid or difluoroacetic acid by the method of Nad et al., Izvest, (1959) page 71; Chem. Abstr. vol. 53, No. 14977; and Vol. 53, No. 17933 (1959).

Formula (2) compounds where R<sub>3</sub> is CH<sub>2</sub>F are obtained by treatment of the Formula (2) compounds where R<sub>3</sub> is CH<sub>3</sub> according to the method of Rozen et al., *Synthesis* (6)665, (1985).

For compounds wherein X is S(O)<sub>m</sub>R<sub>12</sub>, and m is 1 or 2 the final compound 5 is made from the -SR<sub>12</sub> moiety by oxidizing the intermediate -SR<sub>12</sub> product under conditions well known to those skilled in the art, after the appropriate CONH<sub>2</sub> moiety in the synthetic sequence is dehydrated to the cyano moiety. For compounds where X and/or X<sub>3</sub> are Br, I, nitro, amine or formamide, synthesis of these 10 compounds is accomplished by any of the steps described above using a suitably protected amine as X and/or X<sub>3</sub>. Such protecting groups are known to those skilled in the art and are readily disclosed in Greene, T., *Protective Groups in Organic Synthesis*, Wiley Publishers, NY (1981), the contents of which are hereby incorporated by reference. The deprotected amine is then appropriately acylated to the formyl amine moiety, oxidized to the NO<sub>2</sub> moiety, or diazotized and displaced 15 by methods well known to those skilled in the art to produce the desired Br or I moiety.

With appropriate manipulation and protection of any chemical 20 functionalities, synthesis of the remaining compounds of the Formula (I) is accomplished by methods analogous to those above and to those described in the Experimental section. Methods for chiral synthesis of the appropriate compounds of Formula (I) are found in co-pending application No. 07/694,624, which is incorporated by reference herein.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally 25 formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in standard manner for the treatment of the indicated diseases, for example orally, parenterally, sublingually, transdermally, rectally, via inhalation or 30 via buccal administration.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, 35 glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose.

Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may 5 be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, 10 lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

15 A typical suppository formulation comprises a compound of Formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycals, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

20 Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

25 Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

30 Each dosage unit for oral administration contains suitably from 0.001 mg to 100 mg/Kg, and preferably from .01 mg to 30 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. Each dosage unit for intranasal administration or oral inhalation contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I). Each dosage unit for rectal administration contains suitably 0.01 mg to 100 mg of a compound of Formula (I).

35 The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, for example about 0.001

mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 1200 mg/person. The active ingredient may be administered from 1 to 6 times a day, 5 sufficient to exhibit antiinflammatory activity, or if used as a TNF inhibitor, the active ingredient is administered in an amount sufficient to inhibit TNF production such that normal or subnormal levels are achieved which are sufficient to ameliorate or prevent the disease state.

10 The biological activity of the compounds of Formula I as PDE IV inhibitors are demonstrated by the following tests.

Inhibitory Effect of Compounds of Formula I on PDE IV

I. Isolation of PDE Isozymes

15 Phosphodiesterase inhibitory activity and selectivity of compounds is determined using a battery of five distinct PDE isozymes. The characteristics of these PDEs appear in Table 1. The tissues used as sources of the different isozymes are as follows: 1) PDE Ia, canine trachealis; 2) PDE Ib, porcine aorta; 3) PDE Ic, guinea-pig heart; 4) PDE III, guinea-pig heart; and 5) PDE IV, human monocyte. PDEs Ia, Ib, Ic and III are partially purified using standard chromatographic 20 techniques (Torphy and Cieslinski, Mol. Pharmacol. 37:206-214, 1990). PDE IV is purified to kinetic homogeneity by the sequential use of anion-exchange followed by heparin-Sepharose chromatography (Torphy et al., J. Biol. Chem., 267: 1798-1804 (1992)).

25

TABLE 1. Characteristics of PDE isozymes.<sup>a</sup>

Peak	Isozyme	$K_m$ (mM)	
		cAMP	cGMP
Ia	cGMP-specific	135	4
Ib	$Ca^{2+}$ /calmodulin-stimulated	50	5
Ic	$Ca^{2+}$ /calmodulin-stimulated	1	2
III	cGMP-inhibited	0.4	8
IV	Ro 20-1724-inhibited	4	38

<sup>a</sup> Data are from Torphy and Cieslinski, supra.

<sup>b</sup> Nomenclature is from Beavo, Adv. Second Messenger Phosphoprotein Res. 22:1-38, 1988.

II. PDE Assay

Phosphodiesterase activity is assayed as described in Torphy and Cieslinski, Mol. Pharmacol. 37:206-214, 1990. IC<sub>50</sub>s for compounds of this invention range 5 from 25 nM to 500  $\mu$ M.

III. cAMP Accumulation in U-937 Cells

The ability of selected PDE IV inhibitors to increase cAMP accumulation in intact tissues is assessed using U-937 cells, a human monocyte cell line that has been shown to contain a large amount of PDE IV. To assess the activity of PDE IV 10 inhibition in intact cells, nondifferentiated U-937 cells (approximately 10<sup>5</sup> cells/reaction tube) were incubated with various concentrations (0.01-100  $\mu$ M) of PDE inhibitors for one minute and 1  $\mu$ M prostaglandin E2 for an additional four minutes. Five minutes after initiating the reaction, cells were lysed by the addition of 1M potassium carbonate and cAMP content was assessed by RIA. A general 15 protocol for this assay is described in Brooker et al., Radioimmunoassay of cyclic AMP and cyclic GMP, Adv. Cyclic Nucleotide Res., 10:1-33, 1979. Data are expressed as both an EC<sub>50</sub> for increases in cAMP accumulation as a percentage of the maximum response to rolipram produced by 10 mM of the test compounds. EC<sub>50</sub>s for compounds of this invention range from 0.3  $\mu$ M to > 10  $\mu$ M.

20 Inhibitory Effect of Compounds of Formula (I) on TNF Production

I. Inhibitory Effect of compounds of the Formula (I) on in vitro TNF production by Human Monocytes:

The inhibitory effect of compounds of the Formula (I) on in vitro TNF production by Human Monocytes may be determined by the protocol as described in 25 Badger et al., EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

II. In vivo activity

Two models of endotoxin shock have been utilized to determine in vivo TNF activity for the compounds of the Formula (I). The protocol used in these models is 30 described in Badger et al., EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The following examples are given to illustrate the invention. They are not 35 intended to limit the invention in any manner. Reference is made to the claims for what is reserved to the inventors hereunder.

EXAMPLE 1

2-Acetamidopyridine-4-carboxaldehyde

1a) 2-Acetamido-4-picoline To a solution of 2-amino-4-picoline (4.33 g, 40 mmol) in pyridine (50 mL) at 0°C under an argon atmosphere was added dropwise over 15 min, a solution of acetyl chloride (3.3 mL, 46 mmol) in methylene chloride (10 mL). After 0.5 h, the mixture was partitioned between water and methylene chloride, the organic extract was dried over potassium carbonate, filtered and evaporated. Purification by flash chromatography, eluted with 50 % ether/hexanes, provided a white solid : m.p. 99 - 101 °C.

1b) 2-Acetamido-4-picoline-1-oxide A solution of 2-acetamido-4-picoline (1.5 g, 10 mmol) and 3-chloroperbenzoic acid (80%, 2.4 g, 11 mmol) in methylene chloride (20 mL) was stirred at room temperature under an argon atmosphere for 18 h. The mixture was treated with solid sodium bicarbonate, poured into water and extracted three times with methylene chloride. The organic layer was dried over sodium sulfate, filtered and evaporated. The residue was purified by flash chromatography, eluted with 5 % methanol/methylene chloride, to provide a white solid: m.p. 138 - 140 °C.

1c) 2-Acetamido-4-hydroxymethylpyridine A solution of 2-acetamido-4-picoline-1-oxide (1.56 g, 9.39 mmol) in acetic acid (10 mL) was added dropwise over 0.5 h to refluxing acetic anhydride maintained under an argon atmosphere. After stirring at reflux for 1 h after the addition, the mixture was cooled, diluted with water, neutralized with sodium bicarbonate and extracted five times with ethyl acetate. The organic extracts were dried over magnesium sulfate, filtered and evaporated. The residual oil was dissolved in methanol (10 mL), a solution of sodium methoxide in methanol (25%, 12 mL) was added and the mixture was stirred at room temperature for 1 h. After addition of aqueous sodium chloride, the mixture was extracted five times with ethyl acetate, the organic extract was dried over potassium carbonate and evaporated. The residue was purified by flash chromatography, eluting with 5% methanol/methylene chloride, to provide a white solid: m.p. 130 - 132 °C.

1d) 2-Acetamidopyridine-4-carboxaldehyde A solution of 2-acetamido-4-hydroxymethyl-pyridine (645 mg, 3.88 mmol) in pyridine (15 mL) with manganese dioxide (2.36 g, 27.2 mmol) was heated at 105 - 110 °C for 1.5 h, then cooled and filtered through Celite, washing well with methylene chloride. The solvents were evaporated and the residue was purified by flash chromatography, eluting with 50% ethyl acetate/hexanes, to provide a white solid: m.p. 139 - 140 °C.

EXAMPLE 22-Acetamidopyridine-5-carboxaldehyde

2a) Methyl 6-aminonicotinate A solution of 6-aminonicotinic acid (3.31 g, 24 mmol) in methanol (50 mL) and concentrated sulfuric acid (5 mL) under an argon atmosphere was heated at reflux for 16 h. After cooling, the mixture was basified with potassium carbonate, filtered and evaporated. The residue was partitioned between 5% aqueous sodium carbonate and methylene chloride containing 5% methanol, the organic extract was dried over potassium carbonate, filtered and evaporated to provide a white solid : m.p. 158 - 159°C.

10 2b) 2-Amino-5-hydroxymethylpyridine Methyl 6-aminonicotinate (3.52 g, 23.1 mmol) was added in twelve portions over the course of 1 h to a suspension of lithium aluminium hydride (1.76 g, 46.2 mmol) in tetrahydrofuran (100 mL) at 0°C under an argon atmosphere and the mixture was stirred at room temperature for 18 h. An additional quantity of lithium aluminium hydride (0.88 g) was added slowly.

15 The mixture was stirred for 6 h. The mixture was cooled to -78°C and water (2.5 mL), aqueous sodium hydroxide (15%, 2.5 mL) and water (7.5 mL) were added in sequence. The mixture was brought to room temperature, and filtered through Celite. The solid was washed well with 10% methanol/methylene chloride, and the filtrate evaporated. Water was added to the residue and it was extracted several times with 10% methanol/methylene chloride. The organic extracts were dried over potassium carbonate, filtered and evaporated. The residue was purified by flash chromatography, eluting with 7.5% methanol/methylene chloride, to provide a white solid : m.p. 117 - 119°C.

20 2c) 2-Acetamido-5-hydroxymethylpyridine To a solution of 2-amino-5-hydroxymethyl-pyridine (1.09 g, 8.9 mmol) in pyridine (2.15 mL) and methylene chloride (10 mL) at 0°C under an argon atmosphere was added dropwise over 30 min a solution of acetyl chloride (1.6 mL, 22.2 mmol) in methylene chloride (10 mL). After 0.5 h, the mixture was treated with methanol to homogeneity, applied directly to the column and purified by flash chromatography, eluted with 7.5% methanol/methylene chloride, to provide a white solid (1.24 g, 67%): m.p. 85 - 85°C. This solid (1.23g, 5.94 mmol), in methanol (15 mL) was stirred with a solution of sodium methoxide in methanol (25%, 3.25 mL, 14.85 mmol) for 2 h at room temperature under an argon atmosphere. The resultant precipitate was removed by filtration and the filtrate was evaporated. The residue was partitioned between water and 5% methanol/methylene chloride, the organic layer was dried over potassium carbonate, filtered and evaporated to a white solid (845 mg, 86%): m.p. 148 - 150°C.

2d) 2-Acetamidopyridine-5-carboxaldehyde A solution of 2-acetamido-5-hydroxymethyl-pyridine (610 mg, 3.67 mmol) in pyridine (10 mL) was added rapidly to a suspension of pyridinium chlorochromate (1.58 g, 7.34 mmol) in methylene chloride (7 mL) at 0°C under an argon atmosphere. After 0.5 h, ether (50 mL) was added, the mixture was filtered through celite and the filtrate evaporated. The residue was purified by flash chromatography, eluted with 50% ethyl acetate/hexanes, to provide a white solid: m.p. 148 - 149°C.

### EXAMPLE 3

10 Methyl (S)-(+)-4-t-butyloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate

To a solution of (S)-(+)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (152 mg, 0.55 mmol) in dry methylene chloride (2 mL) at room temperature under an argon atmosphere was added triethylamine (0.075 mL, 0.55 mmol), 4-dimethylaminopyridine (67 mg, 0.55 mmol) and di-t-butyldicarbonate (242 mg, 1.09 mmol). After stirring for 1.5 h, the mixture was purified by flash chromatography, eluted with 5% methanol/methylene chloride, to produce a white solid: m.p. 87-89°C. This solid in dry methanol (2 mL) at room temperature under an argon atmosphere was treated with 25% sodium methoxide/methanol (0.125 mL, 0.6 mmol). After stirring for 0.5 h, the mixture was poured into saturated aqueous sodium chloride and extracted three times with methylene chloride. The extract was dried over magnesium sulfate, filtered and evaporated to a white solid: m.p. 73-75°C.  $[\alpha]_D^{25}$  (1.14, methanol) = +0.79.

25 EXAMPLE 4

Methyl (R)-(-)-4-t-butyloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate

To a solution of (R)-(-)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (150 mg, 0.55 mmol) in dry methylene chloride (20 mL) at room temperature under an argon atmosphere was added triethylamine (0.075 mL, 0.55 mmol), 4-dimethylaminopyridine (66 mg, 0.55 mmol) and di-t-butyldicarbonate (245 mg, 1.09 mmol). After stirring for 1.5 h, the mixture was purified by flash chromatography, eluting with 5% methanol/methylene chloride, to produce a white solid: m.p. 83-84°C. This solid in dry methanol (2 mL) at room temperature under an argon atmosphere was treated with 25% sodium methoxide/methanol (0.125 mL, 0.6 mmol). After stirring for 0.5 h, the mixture was poured into saturated aqueous sodium chloride, then extracted three times with methylene chloride. The extract

was dried over magnesium sulfate, filtered and evaporated to a white solid (215 mg, 97%): m.p. 75-77°C.  $[\alpha]_D^{25}$  (1.07, methanol) = -0.65.

#### EXAMPLE 5

5 (R)-1-(2-Acetamido-4-thiazolylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl (R)-4-t-butylloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (239 mg, 0.59 mmol) in chloroform (2.5 mL) at 0°C under an argon atmosphere was treated with trifluoroacetic acid (0.75 mL) and stirred at 10 room temperature for 3.5h. The mixture was neutralized with aqueous sodium bicarbonate and the mixture was extracted three times with chloroform. 2-Acetamido-4-thiazolecarboxaldehyde (105 mg, 0.60 mmol) was added and the mixture was dried over potassium carbonate; the mixture was filtered and evaporated to approximately 5 mL. This mixture was refluxed for 3.5h and then evaporated. 15 The resulting pale yellow foam was dissolved in tetrahydrofuran (1.0 mL) and methanol (1.0 mL). Sodium cyanoborohydride (115 mg, 1.8 mmol) in methanol (1.0 mL) was added followed by the dropwise addition of 0.5 mL of a solution of acetic acid (0.73 mL) in tetrahydrofuran (4.2 mL). The mixture was stirred for one hour under an argon atmosphere, neutralized with sodium bicarbonate and 20 partitioned between water and methylene chloride containing 5% methanol. The organic extract was dried over potassium carbonate and the solvent removed *in vacuo*. Dimethyl sulfoxide (3 mL) and a trace of sodium cyanide were added. The mixture was stirred for 3 hours at 90°C, cooled and was extracted twice with ethyl acetate. The organic extract was washed three times with water and dried over 25 potassium carbonate. Purification by flash chromatography, eluting with 2% methanol/methylene chloride, provided a yellow material: m.p. 71 - 75°C. Analysis Calc. for C<sub>22</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub>S·1/2 H<sub>2</sub>O: C 60.25, H 6.44, N 9.58; found: C 60.32, H 6.62, N 9.31.

30

#### EXAMPLE 6

(S)-1-(2-Acetamido-4-thiazolylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl (S)-4-t-butylloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (249 mg, 0.61 mmol) in chloroform (2.5 mL) at 0°C under 35 an argon atmosphere was treated with trifluoroacetic acid (0.75 mL) and stirred at room temperature for 3h. The mixture was neutralized with aqueous sodium bicarbonate and the mixture was extracted three times with chloroform. 2-Acetamido-4-thiazolecarboxaldehyde (104 mg, 0.61 mmol) was added and the

mixture was dried over potassium carbonate; the mixture was filtered and evaporated to approximately 5 mL. This mixture was refluxed for 4 h and then evaporated. The resulting pale yellow foam was dissolved in tetrahydrofuran (1.0 mL) and methanol (1.0 mL). Sodium cyanoborohydride (114 mg, 1.8 mmol) in methanol (1.0 mL) was 5 added followed by the dropwise addition of 0.5 mL of a solution of acetic acid (0.73 mL) in tetrahydrofuran (4.25 mL). The mixture was stirred for one hour under an argon atmosphere, neutralized with sodium bicarbonate and partitioned between water and methylene chloride containing 5% methanol. The organic extract was dried over potassium carbonate and the solvent removed *in vacuo*. Dimethyl sulfoxide (3 mL) and a trace of sodium cyanide were added. The mixture was 10 stirred for 2 hours at 90°C, cooled and was extracted twice with ethyl acetate. The organic extract was washed three times with water and dried over potassium carbonate. Purification by successive flash chromatography, eluting first with 2.5% methanol/methylene chloride followed by 1.5% methanol/methylene chloride, 15 provided a sticky yellow material. Analysis Calc. for C<sub>22</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub>S·1/10 H<sub>2</sub>O: C 61.26, H 6.36, N 9.74; found: C 61.11, H 6.38, N 9.47.

#### EXAMPLE 7

##### 1-(2-Pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone hydrochloride

20 A solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (275 mg, 1.0 mmol) in dry dimethylformamide (5 mL) was treated with sodium hydride (35 mg, 1.17 mmol of an 80% dispersion) and stirred under an argon atmosphere. After 15 min, 15-crown-5 ether (200mL, 1.007 mmol) was added and the reaction 25 stirred at room temperature for an additional two hours. 2-Picolyl chloride (175 mg, 1.37 mmol) was added. After stirring at room temperature for 16 hours, water was added to the reaction mixture and it was extracted with 9:1 ether/methylene chloride. The organic extract was dried (potassium carbonate) and concentrated *in vacuo* to yield a yellow oil, which was purified by flash chromatography, eluting with 95:5 30 ether/methanol. The resulting oil was dissolved in 9:1 ether/methylene chloride and treated with 0.75 mL of 1.0 M hydrochloric acid in ether to provide the solid hydrochloride salt, which was recrystallized from acetonitrile and ether: m.p. 132-133°C. Analysis Calc. for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>.HCl: C 65.58, H 6.75, N6.95; found: C 65.73, H 6.94, N 7.01.

EXAMPLE 81-(3-Pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone hydrochloride

A solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (275 mg, 1.0 mmol) in dry dimethylformamide (5 mL) was treated with sodium hydride (35 mg, 1.17 mmol of an 80% dispersion) and stirred under an argon atmosphere. After 15 min, 15-crown-5 ether (200 mL, 1.007 mmol) was added and the reaction stirred at room temperature for an additional 2.5 hours. 3-Picolyl chloride (175 mg, 1.37 mmol) was added. After stirring at room temperature for 72 hours, water was added to the reaction mixture and it was extracted with 9:1 ether/methylene chloride. The organic extract was dried (potassium carbonate) and concentrated *in vacuo* to yield a yellow oil, which was purified by flash chromatography, eluting with 94:6 ether/methanol. The resulting oil was dissolved in 9:1 ether/methylene chloride and treated with 0.85 mL of 1.0 M hydrochloric acid in ether to provide the solid hydrochloride salt, which was recrystallized from acetonitrile and ether): m.p. 160-162°C. Analysis Calc. for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>·HCl : C 65.58, H 6.75, N 6.95; found : C 65.83, H 6.88, N 7.05.

EXAMPLE 91-(4-Pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone hydrochloride

A solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (275 mg, 1.0 mmol) in dry dimethylformamide (5 mL) was treated with sodium hydride (35 mg, 1.17 mmol of an 80% dispersion) and stirred under an argon atmosphere. After 15 min, 15-crown-5 ether (200mL, 1.007 mmol) was added and the reaction stirred at room temperature for an additional two hours. 4-Picolyl chloride (175 mg, 1.37 mmol) was added. After stirring at room temperature for 16 hours, water was added to the reaction mixture and it was extracted with 9:1 ether/methylene chloride. The organic extract was dried (potassium carbonate) and concentrated *in vacuo* to yield a yellow oil, which was purified by flash chromatography, eluted with 94:6 ether/methanol. The resulting oil was dissolved in 9:1 ether/methylene chloride and treated with 0.85 mL of 1.0 M hydrochloric acid in ether to provide the solid hydrochloride salt, which was recrystallized from acetonitrile and ether; m.p. 160-163°C. Analysis Calc. for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>·HCl: C 65.58, H 6.75, N 6.95; found : C 65.72, H 6.73, N 7.04.

EXAMPLE 101-[2-(4-Morpholinyl)ethyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone hydrochloride

A solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (200 mg, 0.73 mmol) in dry dimethylformamide (4 mL) was treated with sodium hydride (40 mg, 1.0 mmol of an 60% dispersion) and stirred under an argon atmosphere overnight. 15-crown-5 ether (200 mL, 0.9 mmol) was added to the flask. In a separate flask, 2-chloroethylmorpholine hydrochloride (322 mg, 1.7 mmol) was dissolved in dimethylformamide (1 mL) and treated with sodium hydride (80 mg, 1.0 mmol of a 60% dispersion) to release the free base, and stirred under an argon atmosphere for 1h. The 2-chloroethylmorpholine solution was added to the amide anion and the reaction stirred for 48h. Ice-water was added to the reaction mixture and it was extracted with ethyl acetate/ether/methylene chloride and washed with water. The organic extract was dried (potassium carbonate) and concentrated *in vacuo* to yield a yellow oil, which was purified by flash chromatography, eluting with 85:15 methylene chloride/acetone adding 0.5-6% methanol. The resulting oil was dissolved in ether/methylene chloride and treated with 0.5 mL of 1.0 M hydrochloric acid in ether to provide the solid hydrochloride salt, which was recrystallized from ethyl acetate: m.p. 159-160°C. Analysis Calc. for C<sub>22</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>·HCl·1/4H<sub>2</sub>O : C 61.53, H 7.86, N 6.52, Cl 8.26; found: C 61.28, H 7.63, N 6.37, Cl 8.10.

EXAMPLE 111-(2-Imidazolymethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

25 11a) 1-[2-(1-Benzyl)imidazolymethyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (300 mg, 1.09 mmol) in dry dimethylformamide (3.5 mL) was treated with sodium hydride (70 mg, 1.75 mmol of an 60% dispersion) and 15-crown-5 ether (200 mL, 0.9 mmol) and stirred under an argon atmosphere for 5 h. A solution of the 2-chloromethyl-1-benzylimidazole (289 mg, 1.19 mmol) in dimethylformamide (2 mL) was added and stirred under an argon atmosphere for 2h. Ice-water was added to the reaction mixture and it was extracted with ethyl acetate and washed with water. The organic extract was dried (potassium carbonate) and concentrated *in vacuo* to yield an oil, which was purified by flash chromatography, eluting with 3:1 ethyl acetate/petroleum ether and adding 4-6% isopropanol to provide an oil.

35 11b) 1-(2-Imidazolymethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of 1-[2-(1-benzyl)imidazolymethyl]-4-(3-cyclopentyloxy-

4-methoxyphenyl)-2-pyrrolidinone (225 mg, 0.5 mmol) and 70% perchloric acid (13 drops) were added to a suspension of 10% palladium on carbon (125 mg) in ethanol (50 mL). The mixture was hydrogenated at 50 psi for 60 h, filtered through celite and evaporated. The residue was partitioned between ethyl acetate and 5% aqueous sodium carbonate and extracted three times. The organic layer was dried (potassium carbonate), evaporated *in vacuo* and purified by flash chromatography, eluting with 3:1 ethyl acetate/hexanes, adding 0-10% methanol to provide an oil and recovered starting material which was subjected to the reaction conditions a second time. The two isolated products were combined and were recrystallized from ethyl acetate/ether: m.p. 76-79°C. Analysis Calc. for C<sub>20</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>·1/4H<sub>2</sub>O : C 66.73, H 7.14, N 11.67; found : C 66.67, H 7.16, N 11.76.

#### EXAMPLE 12

(S)-(-)-1-(3-Acetamido-4-pyridylmethyl)-4-(3cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl (S)-4-t-butylloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (251 mg, 0.61 mmol) in chloroform at 0°C under an argon atmosphere was treated with trifluoroacetic acid (0.75 mL) and stirred at room temperature for 3h. The mixture was neutralized with sodium bicarbonate, cold 5% sodium carbonate was added and the mixture was extracted three times with chloroform. 2-Acetamido-4-pyridinecarboxaldehyde (102 mg, 0.61 mmol) was added and the mixture was dried over potassium carbonate; the mixture was filtered and evaporated to approximately 5 mL. This mixture was refluxed for 3.5 h and then evaporated. The resulting pale yellow foam was dissolved in tetrahydrofuran (1.0 mL) and methanol (1.0 mL). Sodium cyanoborohydride (38 mg, 0.61 mmol) in methanol (1.0 mL) was added and, after 10 minutes, 0.5 mL of a solution of acetic acid (0.73 mL) in tetrahydrofuran (5 mL). The mixture was stirred for one hour under an argon atmosphere, neutralized with sodium bicarbonate and partitioned between water and methylene chloride containing 5% methanol. The organic extract was dried over potassium carbonate and the solvent removed *in vacuo* to provide a pale green foam. Dimethyl sulfoxide (3 mL) and a trace of sodium cyanide were added. The mixture was stirred for 2 hours at 90°C, cooled and was extracted twice with ethyl acetate. The organic extract was washed four times with water and dried over potassium carbonate. Purification by flash chromatography, eluting with 2.5% methanol/methylene chloride, provided a white solid: 143 -145°C.

Analysis Calc. for C<sub>24</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub>·1/4H<sub>2</sub>O: C 67.35, H 6.95, N 9.82; found : C 67.26, H 6.92, N 9.73. [a]<sub>D</sub><sup>25</sup> (0.86, methanol) = -32.1.

EXAMPLE 13(S)-(-)-1-(4-Acetamido-3-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

5       A solution of methyl (S)-4-t-butylloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (215 mg, 0.53 mmol) in chloroform (2.5 mL) at 0°C under an argon atmosphere was treated with trifluoroacetic acid (0.75 mL) and stirred at room temperature for 1.5h. The mixture was neutralized with sodium bicarbonate, cold 5% sodium carbonate was added and the mixture was extracted two times with  
10      chloroform. 2-Acetamido-pyridine-5-carboxaldehyde (102 mg, 0.61 mmol) was added and the mixture was dried over potassium carbonate; the mixture was filtered and evaporated to approximately 5 mL. This mixture was refluxed for 4.0 h and then evaporated. The resulting pale orange foam was dissolved in tetrahydrofuran (1.0 mL) and methanol (1.0 mL) under an argon atmosphere. Sodium  
15      cyanoborohydride (100.3 mg) was added with methanol (0.5 ml) and, after 10 minutes, 0.5 mL of a solution of acetic acid (0.6 mL) in tetrahydrofuran (5 mL). After 15 min, the mixture was neutralized with sodium bicarbonate and partitioned between water and methylene chloride containing 5% methanol. The organic extract was dried over potassium carbonate and the solvent removed *in vacuo*. Dimethyl  
20      sulfoxide (2 mL) and a trace of sodium cyanide were added. The mixture was stirred for 3.5 hours at 90°C, cooled, diluted with water and extracted twice with ethyl acetate. The organic extract was washed five times with water and dried over potassium carbonate. Purification by flash chromatography, eluting with 2.5% methanol/methylene chloride, provided a white foam: m.p. 73-75°C. Analysis Calc.  
25      for C<sub>24</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub>·1/8H<sub>2</sub>O: C 67.70, H 6.92, N 9.87; foun: C 67.68, H 6.97, N 9.83. [a]<sub>D</sub><sup>25</sup> (0.80, methanol) = -44.4.

EXAMPLE 14(R)-(+)-1-(3-Acetamido-4-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

30       A solution of methyl (R)-4-t-butylloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (250 mg, 0.61 mmol) in chloroform at 0°C under an argon atmosphere was treated with trifluoroacetic acid (0.75 mL) and stirred at room temperature for 3h. The mixture was neutralized with sodium bicarbonate, cold 5% sodium carbonate was added and the mixture was extracted three times with chloroform. 2-Acetamido-pyridine-4-carboxaldehyde (102 mg, 0.61 mmol) was added and the mixture was dried over potassium carbonate; the mixture was filtered and evaporated to approximately 5 mL. This mixture was refluxed for 3.5 h and

then evaporated. The resulting pale yellow foam was dissolved in tetrahydrofuran (1.0 mL) and methanol (1.0 mL). Sodium cyanoborohydride (38 mg, 0.61 mmol) in methanol (1.0 mL) was added and, after 10 minutes, 0.5 mL of a solution of acetic acid (0.73 mL) in tetrahydrofuran (5 mL). The mixture was stirred for one hour under an argon atmosphere, neutralized with sodium bicarbonate and partitioned between water and methylene chloride containing 5% methanol. The organic extract was dried over potassium carbonate and the solvent removed *in vacuo* to provide a pale green foam. Dimethyl sulfoxide (3 mL) and a trace of sodium cyanide were added. The mixture was stirred for 2 hours at 90°C, cooled and was extracted twice with ethyl acetate. The organic extract was washed four times with water and dried over potassium carbonate. Purification by flash chromatography, eluting with 2% methanol/methylene chloride, provided a white solid: 143 -144°C.

10      Analysis Calc. for C<sub>24</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub>.1/4H<sub>2</sub>O: C 67.34, H 6.95, N 9.82; found: C 67.27, H 6.88, N 9.73. [a]<sub>D</sub><sup>25</sup> (0.92, methanol) = +31.4.

#### EXAMPLE 15

##### (R)-(+)-1-(4-Acetamido-3-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

20      A solution of methyl (R)-4-t-butyloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (215 mg, 0.53 mmol) in chloroform (2.5 mL) at 0°C under an argon atmosphere was treated with trifluoroacetic acid (0.75 mL) and stirred at room temperature for 1.5h. The mixture was neutralized with sodium bicarbonate, cold 5% sodium carbonate was added and the mixture was extracted two times with chloroform. 2-Acetamido-pyridine-5-carboxaldehyde (102 mg, 0.61 mmol) was added and the mixture was dried over potassium carbonate; the mixture was filtered and evaporated to approximately 5 mL. This mixture was refluxed for 4.0 h and then evaporated. The resulting pale orange foam was dissolved in tetrahydrofuran (1.0 mL) and methanol (1 mL) under an argon atmosphere. Sodium cyanoborohydride (100.3 mg) was added with methanol (0.5 ml) and, after 10 minutes, 0.5 mL of a solution of acetic acid (0.6 mL) in tetrahydrofuran (5 mL). After 45 min, the mixture was neutralized with sodium bicarbonate and partitioned between water and methylene chloride containing 5% methanol. The organic extract was dried over potassium carbonate and the solvent removed *in vacuo*. The product was treated with dimethyl sulfoxide (2 mL) with a trace of sodium cyanide and stirred at 85-90°C for 4h. The mixture was diluted with water and extracted twice with ethyl acetate. The organic extract was washed five times with water and dried

over potassium carbonate. Purification by flash chromatography, eluting with 2.5% methanol/methylene chloride, provided a white foam: m.p. 75-77°C.

Analysis Calc. for  $C_{24}H_{29}N_3O_4 \cdot 1/8H_2O$ : C 67.70, H 6.92, N 9.87; found: C 67.52, H 6.89, N 9.89.  $[\alpha]_D^{25}$  (0.86, methanol) = +43.7.

5

#### EXAMPLE 16

##### (R)-1-(2-Acetamido-5-thienylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl (R)-4-t-butyloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (285 mg, 0.70 mmol) in chloroform (2.5 mL) under an argon atmosphere was treated with trifluoroacetic acid (0.75 mL) and stirred at room temperature for 2.5h. The mixture was neutralized with aqueous sodium bicarbonate and the mixture was extracted three times with chloroform. 2-Acetamido-5-thienylcarboxaldehyde (119 mg, 0.70 mmol) and a small amount of ethyl acetate were added and the mixture was dried over potassium carbonate; the mixture was filtered and evaporated. Chloroform was added and this mixture was refluxed for 4 h, stirred at room temperature overnight and then evaporated. The resulting pale yellow foam was dissolved in tetrahydrofuran (1.0 mL) and methanol (1.0 mL). Sodium cyanoborohydride (134 mg, 2.1 mmol) and acetic acid (0.08 mL) were added, the mixture was stirred for two hours under an argon atmosphere, neutralized with sodium bicarbonate and partitioned between water and methylene chloride containing 5% methanol. The organic extracts were dried over potassium carbonate and the solvent removed *in vacuo*. Dimethyl sulfoxide (3 mL) and a trace of sodium cyanide were added. The mixture was stirred for 1.5 hours at 90°C, cooled and was extracted twice with ethyl acetate. The organic extract was washed four times with water, then with brine and dried over potassium carbonate. Purification by successive flash chromatography with 2% methanol/methylene chloride provided a foam. Analysis Calc. for  $C_{23}H_{28}N_2O_4S \cdot 0.5H_2O$ : C 63.14, H 6.68, N 6.40; found: C 63.22, H 6.57, N 6.36.  $[\alpha]_D^{25}$  (1.12, methanol) = +32.95.

30

#### EXAMPLE 17

##### (S)-1-(2-Acetamido-5-thienylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl (S)-4-t-butyloxycarbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (285 mg, 0.70 mmol) in chloroform (2.5 mL) under an argon atmosphere was treated with trifluoroacetic acid (0.75 mL) and stirred at room temperature for 3h. The mixture was neutralized with aqueous sodium bicarbonate and the mixture was extracted three times with chloroform. 2-Acetamido-5-

thienylcarboxaldehyde (118 mg, 0.70 mmol) and a small amount of ethyl acetate were added and the mixture was dried over potassium carbonate; the mixture was filtered and evaporated. Chloroform was added and this mixture was refluxed for 4 h, stirred at room temperature overnight and then evaporated. The resulting pale 5 yellow foam was dissolved in tetrahydrofuran (1.0 mL) and methanol (1.0 mL). Sodium cyanoborohydride (132 mg, 2.1 mmol) and acetic acid (0.08 mL) were added, the mixture was stirred for two hours under an argon atmosphere, neutralized with sodium bicarbonate and partitioned between water and methylene chloride containing 5% methanol. The organic extracts were dried over potassium carbonate 10 and the solvent removed *in vacuo*. Dimethyl sulfoxide (3 mL) and a trace of sodium cyanide were added. The mixture was stirred for 2 hours at 90°C, cooled and was extracted twice with ethyl acetate. The organic extract was washed four times with water, then with brine and dried over potassium carbonate. Purification by successive flash chromatography with 1.75 to 2.5% methanol/methylene chloride 15 provided a foam. Analysis Calc. for C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>S·0.3 H<sub>2</sub>O: C 63.66, H 6.64, N 6.46; found: C 63.66, H 6.58, N 6.36. [a]<sub>D</sub>(25,D) (1.18, methanol) = -33.98.

#### EXAMPLE 18

##### 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(2-methylthioethyl)-2-pyrrolidinone.

20 A solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.3 g, 1.09 mmol) and 15-crown-5 (0.2 mL) in dry dimethylformamide (3.5 mL) under an argon atmosphere at room temperature was treated with sodium hydride (0.055 g of 60% dispersion, 1.36 mmol) for 24h and then 2-chloroethyl methyl sulfide (0.145 mL, 1.46 mmol) was added dropwise. After another 24h, additional sodium hydride 25 (0.55 g of 60% dispersion, 1.36 mmol) was added and, after 2.5h, the mixture was cooled and additional 2-chloroethyl methyl sulfide (0.145 mL, 1.46 mmol) was added dropwise; after 6d at room temperature, these additions were repeated. After 24h, water was added and the mixture was extracted with ethyl acetate. The extract was washed five times with water, was dried (sodium sulfate) and the solvent was 30 removed *in vacuo*. The residue was washed with hexanes and was purified by flash chromatography, eluting with 2-3:1 ethyl acetate/hexanes, to provide an oil. Analysis Calc. for C<sub>19</sub>H<sub>27</sub>NO<sub>3</sub>S·1/4 H<sub>2</sub>O: C 64.47, H 7.83, N 3.94; found: C 64.40, H 7.81, N 4.20.

EXAMPLE 19

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

5 Inhalant Formulation

A compound of formula I, (1 µg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

<u>Tablets/Ingredients</u>	<u>Per Tablet</u>
1. Active ingredient (Cpd of Form. I)	40 mg
2. Corn Starch	20 mg
3. Alginic acid	20 mg
4. Sodium alginate	20 mg
5. Mg stearate	<u>1.3 mg</u> 2.3 mg

10 Procedure for tablets:

Step 1 Blend ingredients No. 1, No. 2, No. 3 and No.4 in a suitable mixer/blender.

15 Step 2 Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3 The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4 The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5 The dry granules are lubricated with ingredient No. 5.

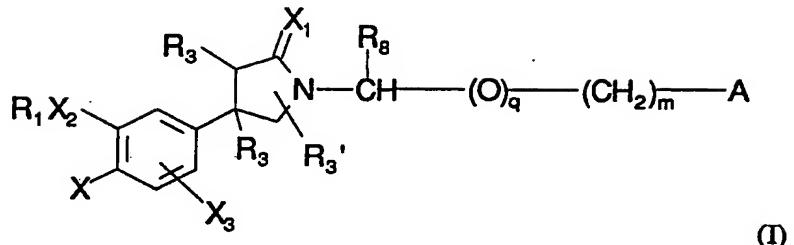
20 Step 6 The lubricated granules are compressed on a suitable tablet press.

Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I in polyethylene glycol 25 with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

## CLAIMS:

1. A compound of the formula:



5

wherein:

R<sub>1</sub> is C<sub>1-12</sub> alkyl unsubstituted or substituted by 1 or more halogens, C<sub>3-6</sub> cycloalkyl unsubstituted or substituted by 1 to 3 methyl groups or an ethyl group; C<sub>4-6</sub> cycloalkenyl containing one or two unsaturated bonds; C<sub>7-11</sub> polycycloalkyl,  
 10 -(CR<sub>14</sub>R<sub>14</sub>)<sub>n</sub>C(O)O-(CR<sub>14</sub>R<sub>14</sub>)<sub>m</sub>-R<sub>10</sub>, -(CR<sub>14</sub>R<sub>14</sub>)<sub>n</sub>C(O)O-(CR<sub>14</sub>R<sub>14</sub>)<sub>r</sub>-R<sub>11</sub>, -(CR<sub>14</sub>R<sub>14</sub>)<sub>x</sub>OH, -(CR<sub>14</sub>R<sub>14</sub>)<sub>s</sub>O(CR<sub>14</sub>R<sub>14</sub>)<sub>m</sub>-R<sub>10</sub>, -(CR<sub>14</sub>R<sub>14</sub>)<sub>s</sub>O(CR<sub>14</sub>R<sub>14</sub>)<sub>r</sub>-R<sub>11</sub>, -(CR<sub>14</sub>R<sub>14</sub>)<sub>n</sub>-(C(O)NR<sub>14</sub>)-(CR<sub>14</sub>R<sub>14</sub>)<sub>m</sub>-R<sub>10</sub>, (CR<sub>14</sub>R<sub>14</sub>)<sub>n</sub>-(C(O)NR<sub>14</sub>)-(CR<sub>14</sub>R<sub>14</sub>)<sub>r</sub>-R<sub>11</sub>, -(CR<sub>14</sub>R<sub>14</sub>)<sub>y</sub>-R<sub>11</sub> or -(CR<sub>14</sub>R<sub>14</sub>)<sub>z</sub>-R<sub>10</sub>;  
 X<sub>1</sub> is O or S;  
 15 X<sub>2</sub> is O or NR<sub>14</sub>;  
 X<sub>3</sub> is hydrogen or X;  
 X is YR<sub>2</sub>, halogen, nitro, NR<sub>14</sub>R<sub>14</sub>, or formamide;  
 Y is O or S(O)m;  
 R<sub>2</sub> is -CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>3</sub>, each may be unsubstituted or substituted by 1 to 5  
 20 fluorines;  
 R<sub>3</sub> is independently hydrogen, halogen, CN, C<sub>1-4</sub>alkyl, halo-substituted C<sub>1-4</sub>alkyl, cyclopropyl unsubstituted or substituted by R<sub>9</sub>, OR<sub>5</sub>, -CH<sub>2</sub>OR<sub>5</sub>, -NR<sub>5</sub>R<sub>16</sub>, -CH<sub>2</sub>NR<sub>5</sub>R<sub>16</sub>, -C(O)OR<sub>5</sub>, -C(O)NR<sub>5</sub>R<sub>16</sub>, -CH=CR<sub>9</sub>R<sub>9</sub>, -C≡CR<sub>9</sub>, or -C(Z)H;  
 R<sub>3'</sub> is hydrogen, halogen, C<sub>1-4</sub>alkyl, halo-substituted C<sub>1-4</sub>alkyl, cyclopropyl  
 25 unsubstituted or substituted by R<sub>9</sub>, -CN, -CH<sub>2</sub>OR<sub>5</sub>, -CH<sub>2</sub>NR<sub>5</sub>R<sub>16</sub>, -C(O)OR<sub>5</sub>, -C(O)NR<sub>5</sub>R<sub>16</sub> or -C(Z)H;  
 A is (2-, 3-, or 4-pyridyl), 4-morpholinyl, 4-piperidinyl, (1-, 2-, 4- or 5-imidazolyl), (2- or 3-thienyl), (2- or 5-pyrimidyl) or (4 or 5-thiazolyl) all of which  
 may be unsubstituted or substituted by one or more: Br, F, Cl, NR<sub>5</sub>R<sub>16</sub>, NR<sub>6</sub>R<sub>16</sub>,  
 30 NO<sub>2</sub>, -COR<sub>7</sub>, -S(O)<sub>m</sub>R<sub>12</sub>, CN, OR<sub>5</sub>, -OC(O)NR<sub>5</sub>R<sub>16</sub>, (1- or 1-(R<sub>5</sub>)-2-imidazolyl),  
 2-imidazolyl, -C(NR<sub>16</sub>)NR<sub>5</sub>R<sub>16</sub>, -C(NR<sub>5</sub>)SR<sub>12</sub>, -OC(O)R<sub>5</sub>, -C(NCN)NR<sub>5</sub>R<sub>16</sub>,  
 -C(S)NR<sub>5</sub>R<sub>16</sub>, -NR<sub>16</sub>C(O)R<sub>15</sub>, oxazolyl, thiazolyl, pyrazolyl, triazolyl or  
 tetrazolyl; or when R<sub>5</sub> and R<sub>16</sub> are as NR<sub>5</sub>R<sub>16</sub> they may together with the nitrogen

form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S; or A is SR<sub>12</sub>;

R<sub>5</sub> is independently hydrogen or C<sub>1-4</sub>alkyl, unsubstituted or substituted by one to three fluorines;

5 R<sub>6</sub> is R<sub>5</sub>, -C(O)R<sub>5</sub>, -C(O)C(O)R<sub>7</sub>, -C(O)NR<sub>5</sub>R<sub>16</sub>, -S(O)<sub>m</sub>R<sub>12</sub>, -C(NCN)S(R<sub>12</sub>), -C(NCN)NR<sub>5</sub>R<sub>16</sub>, -C(NCN)R<sub>12</sub>, -C(NR<sub>16</sub>)R<sub>12</sub> or -C(NR<sub>16</sub>)SR<sub>12</sub>;

R<sub>7</sub> is OR<sub>5</sub>, -NR<sub>5</sub>R<sub>16</sub> or R<sub>12</sub>C(NR<sub>16</sub>)SR<sub>12</sub>;

10 R<sub>8</sub> is hydrogen, C(O)R<sub>7</sub>, (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl-[1,2,3]), (3- or 5-triazolyl-[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl-[1,2,4]), (2-oxadiazolyl-[1,3,4]), (2-thiadiazolyl-[1,3,4]), (2-, 4-, or 5-thiazolyl), (2-, 4-, or 5-oxazolidinyl), (2-, 4-, or 5-thiazolidinyl) or (2-, 4-, or 5-imidazolidinyl), wherein each of the heterocyclic ring systems may be optionally substituted by one or more R<sub>14</sub> groups;

15 R<sub>9</sub> is hydrogen, F or R<sub>12</sub>;

R<sub>10</sub> is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC<sub>1-3</sub>alkyl, halo substituted aryloxyC<sub>1-3</sub>alkyl, indanyl, indenyl, C<sub>7-11</sub> polycycloalkyl, furanyl, pyranyl, thienyl, thiopyranyl, (3- or 4-tetrahydrothiopyranyl), 3-tetrahydrafuranyl, 3-tetrahydrothienyl, (3- or 4-tetrahydropyranyl), C<sub>3-6</sub> cycloalkyl or a C<sub>4-6</sub>cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

20 R<sub>11</sub> is 2-tetrahydropyranyl or 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl or 2-tetrahydrothienyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

25 R<sub>12</sub> is C<sub>1-4</sub>alkyl unsubstituted or substituted by one to three fluorines;

R<sub>14</sub> is independently hydrogen or a C<sub>1-2</sub>alkyl unsubstituted or substituted by fluorine;

30 R<sub>15</sub> is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, or pyrrolyl, and each of the heterocyclics may be unsubstituted or substituted by one or two C<sub>1-2</sub> alkyl groups;

R<sub>16</sub> is OR<sub>5</sub> or R<sub>5</sub>;

35 Z is O, NR<sub>12</sub>, NOR<sub>5</sub>, NCN, C(-CN)<sub>2</sub>, CR<sub>5</sub>NO<sub>2</sub>, CR<sub>5</sub>C(O)OR<sub>5</sub>, CR<sub>5</sub>C(O)NR<sub>5</sub>R<sub>5</sub>, C(-CN)NO<sub>2</sub>, C(-CN)C(O)OR<sub>12</sub> or C(-CN)C(O)NR<sub>5</sub>R<sub>5</sub>;

m is an integer from 0 to 2;

n is an integer from 1 to 4;

q is an integer from 0 to 1;

r is an integer from 1 to 2;  
 s is an integer from 2 to 4;  
 x is an integer from 2 to 6;  
 y is an integer from 1 to 6;  
 5 z is an integer from 0 to 6;  
 or a pharmaceutically acceptable salt thereof;  
 provided that m is 2 when R<sub>10</sub> is OH in -(CR<sub>14</sub>R<sub>14</sub>)<sub>n</sub>-C(O)O-  
 (CR<sub>14</sub>R<sub>14</sub>)<sub>m</sub>R<sub>10</sub>, -(CR<sub>14</sub>R<sub>14</sub>)<sub>n</sub>(C(O)NR<sub>14</sub>)(CR<sub>14</sub>R<sub>14</sub>)<sub>m</sub>R<sub>10</sub> or  
 C(R<sub>14</sub>R<sub>14</sub>)<sub>s</sub>O(CR<sub>14</sub>R<sub>14</sub>)<sub>m</sub>R<sub>10</sub>, and further provided that z is 2 to 6 when R<sub>10</sub> is  
 10 OH in -(CR<sub>14</sub>R<sub>14</sub>)<sub>z</sub>R<sub>10</sub>, and further provided that m is 1 or 2 when A is SR<sub>12</sub>.

2. A compound of claim 1 wherein X<sub>1</sub> and X<sub>2</sub> are oxygen; A is an  
 optionally substituted 2, 3 or 4-pyridyl, 4-morpholinyl, 2-thienyl, 2-imidazolyl or 4-  
 thiazolyl; X is YR<sub>2</sub>; Y is O; R<sub>1</sub> is CH<sub>2</sub>-cyclopropyl, CH<sub>2</sub>-C<sub>5-6</sub> cycloalkyl, C<sub>4-6</sub>  
 cycloalkyl, phenyl, tetrahydrofuran-3-yl, cyclopentenyl, -C<sub>1-2</sub>alkyl optionally  
 15 substituted by one or more fluorines, -(CH<sub>2</sub>)<sub>n</sub>C(O)-O-(CH<sub>2</sub>)<sub>m</sub>CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>s</sub>O(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>,  
 -(CH<sub>2</sub>)<sub>2-4</sub>OH; R<sub>2</sub> is a C<sub>1-2</sub>alkyl optionally substituted by one or more fluorines;  
 one R<sub>3</sub> is hydrogen and the other R<sub>3</sub> is hydrogen, C≡CR<sub>9</sub>, CN, C(Z)H, CH<sub>2</sub>OH,  
 CH<sub>2</sub>F, CF<sub>2</sub>H, or CF<sub>3</sub>; Z is O or NOR<sub>5</sub>; R<sub>3</sub> is hydrogen; and X<sub>3</sub> is hydrogen.

3. A compound of claim 1 wherein R<sub>1</sub> is C<sub>1-4</sub> alkyl substituted by 1 or  
 20 more fluorines, CH<sub>2</sub>-cyclopropyl, CH<sub>2</sub>-cyclopentyl, cyclopentyl or cyclopentenyl;  
 R<sub>2</sub> is methyl or fluoro substituted C<sub>1-2</sub> alkyl; R<sub>3</sub> is hydrogen, C≡CH or CN; and A  
 is 2, 3 or 4-pyridyl, 4-morpholinyl, 2-thienyl, 2-imidazolyl or 4-thiazolyl, all of  
 which may be unsubstituted or substituted by NR<sub>5</sub>R<sub>16</sub> or NR<sub>5</sub>C(O)R<sub>5</sub>.

4. A compound of claim 1 wherein R<sub>1</sub> is cyclopentyl, CF<sub>3</sub>, CH<sub>2</sub>F,  
 25 CHF<sub>2</sub>, CF<sub>2</sub>CHF<sub>2</sub>, CH<sub>2</sub>CF<sub>3</sub>, CH<sub>2</sub>CHF<sub>2</sub>, CH<sub>3</sub>, CH<sub>2</sub>-cyclopentyl, CH<sub>2</sub>-cyclopropyl  
 or cyclopentenyl; R<sub>2</sub> is CH<sub>3</sub>, CF<sub>3</sub>, CHF<sub>2</sub>, or CH<sub>2</sub>CHF<sub>2</sub>; one R<sub>3</sub> is hydrogen and the  
 other R<sub>3</sub> is hydrogen, C≡CH or CN and is in the 4-position.

5. A compound of claim 1 selected from the group consisting of:  
 1-(2-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-  
 30 pyrrolidinone;  
 1-(3-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-  
 pyrrolidinone;  
 1-(4-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-  
 pyrrolidinone;  
 35 1-[2-(4-morpholinyl)ethyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-  
 pyrrolidinone;  
 1-(2-imidazolymethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-  
 pyrrolidinone;

(S)-(-)-1-(3-acetamido-4-pyridylmethyl)-4-(3cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

(S)-(-)-1-(4-acetamido-3-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

5 (R)-(+)-1-(3-acetamido-4-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

(R)-(+)-1-(4-acetamido-3-pyridylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

(S)-(-)-1-(2-acetamido-4-thiazolylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

10 (R)-(+)-1-(2-acetamido-4-thiazolylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

S-(-)-1-(2-acetamido-5-thienylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone; and

15 R-(+)-1-(2-acetamido-5-thienylmethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone; and

4-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-methylthioethyl)-2-pyrrolidinone.

6. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

8. A method for the inhibition of the production of tumor necrosis factor (TNF) in a mammal in need thereof, including humans, which comprises administering to the mammal in need thereof, an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

25 9. A method of treatment of allergic and inflammatory diseases which comprise administering to a subject in need thereof, an effective amount of a compound of claim 1.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/08611

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) <sup>b</sup>			
According to International Patent Classification (IPC) or to both National Classification and IPC			
Int.C1.5	C 07 D 401/06	C 07 D 403/06	C 07 D 409/06
C 07 D 413/06	A 61 K 31/40	A 61 K 31/38	A 61 K 31/41
II. FIELDS SEARCHED			
Minimum Documentation Searched <sup>7</sup>			
Classification System	Classification Symbols		
Int.C1.5	C 07 D	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>			
III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup>			
Category <sup>a</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>		Relevant to Claim No. <sup>13</sup>
X	US,A,4476311 (THE PURDUE FREDERICK COMPANY) October 1984 see column 1, line 32 - column 2, line 25 the entire document *		1-9
Y	---		1-8
Y	WORLD PATENTS INDEX Week 7636, Derwent Publications Ltd., London, GB; AN 76-67577X & JP,A,51 082 258 (YOSHITOMI PHARM. IND. KK) 20 July 1976 see abstract ---		1-8
A	EP,A,0114033 (CIBA-GEIGY AG) claims * see page 6, line 28 - page 7, line 14 ---		1-8
A	EP,A,0350437 (SCHERING AG) claims * ---		1-8
			-/-
IV. CERTIFICATION			
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report		
21-12-1992	28.01.93		
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer  Natalie Weinberg		

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0439766 (ARZNEIMITTELWERK DRESDEN) August 1991 claims * ---	1-8
A	FR,A,2100946 (UCB) claims * ---	1-8
A	EP,A,0270093 (TANABE SEIYAKU CO., LTD.) 1988 see claim 4 ---	1-8
A	CHEMICAL ABSTRACTS, vol. 101, no. 25, 17 December 1984, Columbus, Ohio, US; abstract no. 230442, M. KOBAYASHI ET AL.: 'Studies on the synthesis of antiulcer agents. I. Synthesis and antiulcer activity of imide derivatives' page 763 ; see abstract & Yakugaku Zasshi 104 (6) 652-8 (1984) ---	1-3
A	CHEMICAL ABSTRACTS, vol. 114, no. 11, 18 March 1991, Columbus, Ohio, US; abstract no. 101601, T. A. VORONINA ET AL.: 'Synthesis and pharmacological properties of amidine analogs of pyracetam' page 710 ; see abstract & Khim.-Farm. Zh. 24 (11) 26-9 (1990) -----	1-3

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US 92/08611

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
**Remark: Although claims 8,9 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.**
2.  Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9208611  
SA 65706

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 19/01/93. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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